

## BRUCELLOSIS AND HEART DISEASE

### II. FATAL BRUCELLOSIS: A REVIEW OF THE LITERATURE AND REPORT OF NEW CASES

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In 1941 the senior author encountered at necropsy a case of active brucellosis complicated terminally by signs of aortic valve disease (case 9). Acute endocarditis was suspected clinically; however, the necropsy examination revealed an essentially chronic lesion of the aortic valve. Was this the usual form of brucellar endocarditis? It was not possible to find the answer in standard texts since proved cases are rare. When the periodical literature on brucellar endocarditis was explored, the findings were of such interest and the implications appeared to be of such significance that the investigation was expanded to a review of the world literature on fatal brucellosis.

For this study we have read in the original all the case records we could find purporting to be instances of fatal brucellosis. In a few instances, reports not available in the original are quoted from another source; these are clearly designated in the references. Added to these are a number of previously unpublished cases from several sources, chiefly from the files of the Armed Forces Institute of Pathology; these new cases are reported briefly in the appendix.

All cases have been assigned to one of the following groups:

Group 1. Fatal *Brucella abortus* infection, with adequate necropsy data.

Group 2. Fatal *Brucella melitensis* infection, with adequate necropsy data.

Group 3. Fatal *Brucella suis* infection, with adequate necropsy data.

Group 4. Fatal *Brucella* infection, exact strain uncertain, with adequate necropsy data.

Group 5. Fatal probable brucellosis, with adequate necropsy data.

Group 6. Cases reported as fatal brucellosis, not included in other groups.

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TABLE I  
FATAL *Brucella abortus* INFECTIONS, WITH ADEQUATE NECROPSY DATA (GROUP 1)

Case	Reported by	Origin	Age at death (yr.)	Sex	Duration of symptoms (mo.)	Previous carditis	Endocarditis	Embolic phenomena	Valves affected	Valve lesion	Myocardial aneurysm or abscess	Other myocardial lesions	Mode of death	Comments
1	Matzdorff <sup>3</sup>	Germany	37	M	4 (?)	"Heart trouble"	Yes	Kidney	Aortic	Hyaline	Yes	Resembled Aschoff bodies	Febrile state	
2	Steyrer <sup>4</sup>	Austria	28	M	11	No	Yes	Kidney, spleen	Aortic	Not described	No		Cardiac	Perforated cusps; pericarditis
3	Rothmann <sup>4</sup>	Germany	61	M	3	No	Yes	Spleen	Aortic	Not calcified	No	Granulomas	Cardiac	Granulomas, liver and kidney
4	Rennie & Young <sup>4</sup>	Great Britain	47	M	4	No	Yes	Spleen, liver	Mitral	Calcified	No		Not stated	
5	Sprunt & McBryde <sup>4</sup>	North Carolina	4	M	25	No	No				No		<i>Staph. aureus</i> bacteremia	Aplastic anemia; cellulitis of neck
6	Smith & Curtis <sup>7</sup>	Michigan	47	M	6	"Heart disease"	Yes	Petechiae	Aortic, tricuspid	Calcified	Yes		Febrile state	Large cells in endocardium resembling "Aschoff cells"
7	Spink & Nelson <sup>8</sup>	Minnesota	29	M	8	No	Yes	Petechiae	Aortic	Calcified	Yes	Granulomas	? Cardiac	Cardiac fluoroscopy suggested aortic stenosis
8	Spink Titrud & Kabler <sup>9</sup>	Minnesota	36	M	4	"Heart leakage"	Yes	Spleen, brain	Aortic, mitral	Calcified	No	Resembled Aschoff bodies	Cardiac	Perforated valve
9	Wechsler & Gustafson <sup>10</sup>	New York (or So. America?)	28	M	3 (or 144?)	"Heart attack"	Yes	Spleen; petechiae	Aortic	Hyaline	Yes		Febrile state	"Congenital bicuspid aortic valve"; perforated valve

10	Call et al. <sup>11</sup>	Minnesota	27	M	2 (or 90?)	Rheumatic fever	Yes	No	Aortic	Cardiac, febrile
11	Ibid	Minnesota	49	M	12 (or 168?)	Polyarthritia, fever	Yes	Petechiae	Aortic, mitral	Cardiac
12	Quintin & Stalker <sup>12</sup>	Canada	26	M	11	? Rheumatic fever	Yes	Spleen, ? brain; petechiae	Aortic, mitral	Cardiac, embolism
13	Voth <sup>13</sup>	Kansas	54	M	6	"Heart disease"	Yes	Petechiae; spleen, kidney	Aortic, mitral	Cardiac, shock
14	Hart, Morgan & Lacey <sup>14</sup>	Great Britain	48	M	17	"Bad heart"	Yes	Spleen, kidney	Aortic	Cardiac
15	Purriel et al. <sup>15</sup>	Uruguay	adult	M	4	No	Yes	No	Aortic	Cardiac
16	Spink <sup>16</sup>	Minnesota	33	M	32	No	Yes	Kidney, spleen	Aortic	Not stated
17	Grant & Stote <sup>17</sup>	England	51	M	6	No	Yes	No	Aortic	Cardiac
18	Peery & Belter	Maryland	63	M	15	Dyspnea	Yes	Petechiae; spleen, heart, brain	Aortic, mitral	Cardiac tamponade
19	Peery & Belter	Tennessee	54	M	30	No	Yes	No	Aortic	Cardiac
20	Peery & Belter	Oregon	59	M	2½ (or 86?)	No	Yes	Spleen	Aortic	Cardiac
							Yes	Interstitial fibrosis	Sudden collapse	Thrombosis or embolism, coronary artery

Those cases in which the diagnosis was culturally proved and confirmed by necropsy (groups 1 to 4) have been separated from the other cases and serve as the basis for our conclusions. The paucity of reported cases is somewhat surprising. This is undoubtedly due to a combination of factors: knowledge of brucellosis is almost confined to the last 60 years<sup>1</sup>; the diagnosis of brucellosis is difficult to establish; and few patients die of brucellosis.

#### SUMMARY OF NECROPSY OBSERVATIONS IN FATAL BRUCELLOSIS

Including the new cases described in this report, we have found 20 culturally proved examples of fatal infection due to *Brucella abortus* in which necropsy data are adequate (group 1; Table I). The age distribution is as follows: 4 years, 1 case; 21 to 40 years, 8 cases; 41 to 60 years, 8 cases; 61 years or older, 2 cases. All patients in this group were males. The average duration of symptoms was about 9 months. All except one showed evidence of endocarditis. The sole exception is the case reported by Sprunt and McBryde<sup>6</sup>; death in this 4-year-old boy should, perhaps, be ascribed to aplastic anemia and staphylococcus cellulitis of the neck, but the authors reported the recovery of *Brucella abortus* from postmortem cultures of the spleen and liver. In 15 instances there was necropsy evidence of embolism from the vegetations, but in only 7 were petechiae noted, either during life or at necropsy. Among the 19 cases showing endocarditis, the aortic valve was involved in 18 instances, the mitral valve in 6, and the tricuspid valve in 1. There was a striking tendency toward calcification of the affected valve, this having been specifically noted in 13 cases (68 per cent); in 3 other instances, the valve was described as hyaline or sclerotic. There was perforation of a valve cusp in 5 cases. In 11, abscesses or aneurysms of the myocardium were noted, usually continuous with the valvular vegetation. Other inflammatory lesions of the heart were noted in 10 cases; in 4 of these the authors noted the resemblance of the myocardial lesions to the Aschoff bodies described in rheumatic fever. In 2 instances there was involvement of the pericardium. Although granulomatous lesions were occasionally noted in other organs in this group, the serious lesions were confined largely to the heart. In at least 11 cases, death was thought to be a result of cardiac failure or decompensation.

There are 13 examples of fatal *Brucella melitensis* infection, proved by culture, in which the necropsy record was adequate (group 2; Table II). The youngest patient was 15 years old; the remainder were 28 to 54 years of age. Ten were males and 3 were females. The average duration of symptoms was about 6 months. In the 13 cases there are 9 instances of endocarditis. The exceptions were a 15-year-old boy reported

by Amuchastegui and Herrero<sup>23</sup> and 3 females reported by Arias.<sup>25</sup> In 8 of the 9 cases of endocarditis there was necropsy evidence of embolism from the valvular vegetations, and petechiae were observed in 6 cases. The affected valve cusps were perforated in 4 instances. The infectious process involved the aortic valve in 5 cases, the mitral valve in 4, and the pulmonic valve in 1. Again there was a tendency toward calcification and healing in the valve lesions; in 2 instances calcium deposits were specifically mentioned, and in 5 others the lesions were described as old, hyaline, sclerotic, or thickened. In 2 cases there was an abscess in the myocardium. In 5 instances cellular infiltration of the myocardium was described; in one of these a resemblance to Aschoff bodies was noted. There was pericardial involvement in 4 cases. In one instance death was due to massive peritoneal hemorrhage, presumably from a mycotic aneurysm, although none was found. The 3 cases reported by Arias,<sup>25</sup> all females, were said to show hepatitis; in 1 additional case there was evidence of cirrhosis of the liver. Inflammation of the brain and meninges was described in 2 cases. In 6 instances, death was ascribed to cardiac failure.

Only 7 cases of fatal *Brucella suis* infection, proved by culture, could be found for inclusion in group 3 (Table III). All of these were from the United States. They were males ranging in age from 21 to 62 years. In 2 the illness was a brief septicemia with no particular organ localization; in the 5 other cases symptoms were present for 4 to 84 months. Valvular heart lesions were noted in 3 cases, and in 2 of these the valve cusps were perforated. Embolism from the vegetations occurred in 2 of the 3 cases of endocarditis; petechiae were observed in none. The aortic valve and the mitral valve were each involved twice by the infectious process. Calcification in the valve cusps was not specifically described, but in 2 cases the valvular lesions were noted to be fibrotic. An abscess of the myocardium was encountered in 1 case. Myocardial lesions were noted in only 1 case.<sup>31</sup> In 2 cases, only 1 of which was described as showing endocarditis, death was due to rupture of an arterial aneurysm (basilar, femoral). In 1 case death was due to cardiac decompensation.

There are 4 cases in group 4 (Table IV), in which the *Brucella* was cultured but was not identified as to strain. In each there was adequate necropsy data. The ages ranged from 21 to 54 years. Again all cases were males. The duration of symptoms was somewhat uncertain. Endocarditis was present in all 4. Embolic phenomena occurred in all with the possible exception of case 4. Petechiae were noted in 3 cases. The aortic valve was affected in every instance, the mitral valve in 3. The valve cusps were perforated in 2 cases. In 1 case the valve cusps were described as calcified; in 2 others they were hard or rigid. An aneurysm

TABLE II  
FATAL *Brucella melitensis* INFECTIONS, WITH ADEQUATE NECROPSY DATA (GROUP 2)

Case	Reported by	Origin	Age at death (yr.)	Sex	Duration of symptoms (mo.)	Previous carditis	Endocarditis	Embolic phenomena	Valves affected	Valve lesion	Myocardial aneurysm or abscess	Other myocardial lesions	Mode of death	Comments
1	De la Chappelle <sup>18</sup>	Italy or New York (?)	38	M	7	No	Yes	Petechiae; spleen, toe	Aortic	Hyaline	No		Hemorrhage	Pericardial effusion; hemoperitoneum (from mycotic aneurysm?)
2	Casanova & Ignazio <sup>19</sup>	Italy	28	M	9	No	Yes	Petechiae; spleen, kidney	Aortic	Old	No		Cardiac	
3	Silbergleit <sup>10</sup>	Italy	30	M	2	No	Yes	Lungs	Mitral, pulmonic	Not stated	No		Cardiac	Pericardial effusion; perforated valve
4	Levy & Singerman <sup>21</sup>	Vermont or Connecticut (?)	54	M	2½	Dyspnea	Yes	Petechiae; spleen, kidney	Mitral	Fibrous	No		Febrile state	Jaundice
5	Posteli et al. <sup>22</sup>	Italy	54	M	2	No	Yes	Petechiae	Aortic	Not stated	No		Cardiac	Perforated cusp; cirrhosis

6	Amuchaste- gui & Herrero <sup>33</sup>	Argentina	15	M	14	No	No	No	No	Interstitial inflammation	Febrile state	Bronchiectasis; spleen 1,140 gm.
7	Ibid	Argentina	42	M	?14	No	Yes	Spleen, kidney	Aortic	Calcified	Yes	Pericarditis; per- forated cusp
8	Beebe & Mencely <sup>34</sup>	New York	31	M	12	Rheumatic fever	Yes	Petechiae	Aortic	Sclerotic	No	Pericarditis; per- forated cusp
9	Arias <sup>35</sup>	Peru	47	F	?2	No	No	No	No	Interstitial inflammation	Hepatic coma	Subacute atrophy of liver; meningo- encephalitis
10	Ibid	Peru	30	F	1/2	No	No	No	No	Interstitial inflammation	Febrile state	"Brucellic hepatitis"; pneumonia
11	Ibid	Peru	34	F	?2	No	No	No	No	Interstitial inflammation	Febrile state	"Brucellic hepatitis"; pneumonia
12	Peery & Belter	Texas	48	M	10	No	Yes	Petechiae; spleen, kidney	Mitral	Calcified	No	Pneumonia; pul- monary infarcts
13	Peery & Belter	Texas & Mexico	43	M	4	No	Yes	Mitral	Thickened	Yes	Febrile, cardiac	Jaundice, sulfa therapy

TABLE III  
FATAL *Brucella suis* INFECTIONS, WITH ADEQUATE NECROPSY DATA (GROUP 3)

Case	Reported by	Origin	Age at death (yr.)	Sex	Duration of symptoms (mo.)	Previous carditis	Endocarditis	Embolic phenomena	Valves affected	Valve lesion stated	Myocardial aneurysm or abscess	Other myocardial lesions	Mode of death	Comments
1	Hardy et al. <sup>16</sup>	Iowa	21	M	4	No	Yes	Brain	Aortic	Not stated	Yes		Cardiac	Valve cusps destroyed
2	Hanemann & Schenker <sup>17</sup>	Iowa	24	M	11	No	No				No		CNS hemorrhage	Ruptured aneurysm, basilar artery; meningo-encephalitis
3	Menafee & Poston <sup>18</sup>	North Carolina	26	M	25	No	No				No		Febrile state	Jaundice; granulomas, parenchymatous organs
4	De Gowin et al. <sup>19</sup>	Iowa	45	M	10	No	Yes	Spleen	Mitral	Fibrosis	No		Hemorrhage	Ruptured aneurysm, femoral artery; ruptured valve cusp; nephritis
5	Meyer <sup>20</sup>	California	24	M	1/3	No	No				No		Febrile state	Micro-abscesses in various organs
6	Lowbeer <sup>21</sup>	Oklahoma	62	M	84	No	Yes		Mitral, aortic	Fibrotic	No	Scattered areas of fibrosis	Febrile state	Osteomyelitis, hip and pelvis
7	Peery & Belter	North Carolina	60	M	1/3	No	No				No		Febrile state	

TABLE IV  
FATAL BRUCELLA INFECTIONS, EXACT STRAIN UNCERTAIN, WITH ADEQUATE NECROPSY DATA (GROUP 4)

Case	Reported by	Origin	Age at death	Sex	Duration of symptoms (mo.)	Previous carditis	Endocarditis	Embolic phenomena	Valves affected	Valve lesion	Myocardial aneurysm or abscess	Other myocardial lesions	Mode of death	Comments
1	Scott & Saphir <sup>23</sup>	Ohio	21	M	10	Rheumatic fever	Yes	Petechiae; spleen, brain (?)	Aortic, mitral	Rigid; acute and chronic	No	Interstitial inflammation	Febrile state	Pericardial adhesions
2	Puech et al. <sup>22</sup>	France	25	M	3 (or 39?)	"Articular rheumatism"	Yes	Petechiae	Aortic, mitral	Hard vegetations	No	Interstitial inflammation	Cardiac	Pericarditis; perforated valve cusps; uremia
3	Gounelle & Warter <sup>24</sup>	Tunisia	45	M	3	No	Yes	Petechiae; kidney	Aortic	Ulcerative	Yes		Cardiac	Perforated valve cusps; pericarditis
4	Peery & Belter	Massachusetts	54	M	2 (or 11?)	Heart murmur	Yes	Heart (?)	Aortic, mitral	Calcified	No	Old infarct, granulomas like Aschoff bodies	Febrile state	Coronary thrombosis (embolism?)

of the myocardium was noted in 1. Two others showed evidence of myocarditis, and in the fourth there was an old myocardial infarct, possibly embolic in origin. There was pericardial involvement in 3 cases. In 2 instances, death was ascribed to cardiac failure.

Group 5 comprises 15 cases (Table V) reported as fatal brucellosis, where the diagnosis was based on a serum agglutination titer of 1:500 or above, rather than on culture. In some of these cases cultures were negative; in others they were not done. In all other respects these cases were satisfactory for evaluation. The youngest patient was 19 years of age. The remainder ranged from 24 to 67 years. All but 2 were males. The average duration of symptoms was approximately 13 months. Endocarditis was described in 10 of the 15 cases, and in 3 the valve cusps were said to be eroded or perforated. Embolism from the vegetations occurred in 9 instances, but petechiae were noted in only 2. The aortic valve was involved in 7 instances, the mitral in 4; in 1 case the affected valve was not named. There was a specific description of calcification of the valve cusps in 2 cases; in 5 others the valves were described as gritty, fibrotic, sclerotic or hyaline. An aneurysm of the myocardium was noted in 1 case, and other myocardial lesions were described in 6 cases. In 2 of these a resemblance to Aschoff bodies was noted; in a third the lesions were like Bracht-Wächter bodies. In 5 instances there was pericarditis. In 10, death was apparently a result of cardiac failure; in 2 there was myocarditis but no endocarditis.

Group 6 is composed of those cases considered by their authors to be instances of fatal brucellosis but excluded from the other groups for one reason or another. In some the diagnosis of brucellosis is considered uncertain or even unlikely; in others it appears that some disease unrelated to brucellosis was the cause of death; in many there was either no necropsy or the description of the necropsy was inadequate for our purposes. These 86 cases\* are not considered further in this analysis.

## DISCUSSION

There are, then, 44 cases in groups 1 to 4 in which the diagnosis of brucellosis was established by culture. In each, death was a result of the infection or of complications therefrom, and an adequate necropsy report was available. In these cases there was some form of carditis in 38 instances (86 per cent). Endocarditis was by far the most important manifestation, being present in 35 instances (80 per cent). The incidence of endocarditis was highest in fatal infections due to *Brucella*

\* References 44 to 63 cite most of the cases in group 6. The following authors, some of whose cases have been listed in other groups, are also represented in group 6: Hardy and colleagues,<sup>44</sup> 9 cases; Curschmann,<sup>45</sup> 2 cases; Lowbeer,<sup>46</sup> 3 cases; Arias,<sup>47</sup> 3 cases.

*abortus* (95 per cent). In the *Brucella melitensis* group, endocarditis was found in 69 per cent, and in the *Brucella suis* group, in 43 per cent.

The endocardial lesions of brucellosis appear to be a result of direct invasion of the valves by the infecting organisms. The micro-abscesses within the valve cusps, the destruction of the commissures, and the nodular, calcific nature of the deformity indicate that this is a chronic bacterial endocarditis. There was nothing about the lesions to suggest a hypersensitivity reaction; eosinophils were lacking and there was no evidence of arteritis.

Brucellar endocarditis may apparently develop on previously normal valves, if this can be inferred by the absence of cardiac symptoms and signs before the onset of brucellosis. Among the 35 cases of brucellar endocarditis in the culturally proved group, there was a prior history of rheumatic fever, heart disease, or dyspnea in only 15 (43 per cent). In the patients in whom there was such a history, it was often impossible to determine whether the symptoms were actually due to previous rheumatic fever or to earlier attacks of brucellosis.

There is a specific but not exclusive affinity of the *Brucella* for the aortic valve. Among the 35 instances of endocarditis at necropsy, the aortic valve was involved in 29 (83 per cent). The mitral valve was affected in 15 (45 per cent). The affinity for the aortic valve was particularly remarkable among the infections due to *Brucella abortus*; in this group the aortic valve was involved in 95 per cent of the cases showing endocarditis, and the mitral valve in 32 per cent.

Another noteworthy feature of the endocarditis due to *Brucella* is the frequency of calcification of the affected cusps and of the vegetations themselves. Among the 35 cases of endocarditis, calcification was specifically mentioned in 16 (46 per cent). This feature was particularly common in endocarditis due to *Brucella abortus*, in which calcification was specifically noted in 13 cases (68 per cent). Calcification has also been noted in the lesions of brucellosis in other organs, in both experimental animals and in man.<sup>31,64-66</sup>

Embolism and infarction stemming from valve vegetations seem to be less frequent in brucellar endocarditis than in that due to other organisms. There was necropsy evidence of embolism of the internal organs in 63 per cent of the 19 cases of endocarditis due to *Brucella abortus*, and of petechiae of the skin in 37 per cent. Focal embolic glomerulonephritis was extremely uncommon.

A remarkable feature of fatal brucellar endocarditis is that, at least in these cases, it is exclusively a disease of males (100 per cent).

Patients dying of brucellar endocarditis are older on the average than those who die with other forms of bacterial endocarditis. The cases

TABLE V  
FATAL PROBABLE BRUCELLOSIS, WITH ADEQUATE NECROPSY DATA (GROUP 5)

Case	Reported by	Origin	Age at death (yr.)	Sex	Duration of symptoms (mo.)	Previous carditis	Agglutination	Endocarditis	Embolic phenomena	Valves affected	Valve lesion	Myocardial aneurysm or abscess	Other myocardial lesions	Mode of death	Comments
1	Ivarsson <sup>16</sup>	Denmark	42	M	2		1:5000	No							Thrombosis, femoral veins; intestinal hemorrhage
2	Ebskov & Harpøth <sup>18</sup>	Denmark	19	M	7+	No	1:1600	Yes	No	Aortic	Not stated	No	Not stated	Cardiac	Anemia; nephritis; pericarditis
3	Curschmann <sup>17</sup>	Germany	65	M	2		1:1600	No				No	Subacute myocarditis	Cardiac	Purulent pericarditis; pulmonary emboli
4	Wohlwill <sup>18</sup>	Germany	67	F	1		1:3200	No				No	No	Sudden	Pulmonary emboli
5	Harkness <sup>19</sup>	Great Britain	32	M	32	No	1:784	Yes	Petechiae; kidney, spleen	Mitral, aortic fibrotic	"Gritty,"	No	Not stated	Cardiac	
6	Werthemann <sup>10</sup>	Switzerland	34	M	5	Heart murmurs	1:800	Yes	Spleen	Aortic	Calcified	No	Myocarditis	Cardiac	Pericarditis; encephalomenigitis

7	Raynaud et al. <sup>41</sup>	Algiers	50	M	4	No	1:500	Yes	Spleen, kidney	Aortic	Fibrotic	No	Not stated	Uremia	Spleen, 1,300 gm.
8	Spivak & Cerepnina <sup>42</sup>	Russia	30	F	24 (?)	No	1:1600	Yes	Spleen, kidney	Not stated	Not stated	No	"Ulcerating myocarditis"	Cardiac	Pericarditis; periarteritis
9	Stigliani <sup>43</sup>	Italy	26	M	72	No	1:1500	Yes	Spleen, brain	Mitral	Sclerotic	No	Bracht-Wächter bodies	Not stated	
10	Ibid	Italy	46	M	?	No	1:2000	Yes	Brain	Aortic	Not fibrotic	No	Not stated	Cardiac	Cusp eroded
11	Peery & Belter	Illinois (or Great Britain?)	25	M	7		1:100000	No				No	Like Aschoff bodies	Cardiac	Thrombophlebitis, mural thrombi
12	Peery & Belter	Virginia	51	M	18	No	1:10240	Yes	Spleen, kidney, mesentery	Aortic	Hyaline	No	No	Febrile, cardiac	Pulmonary infarct, ruptured aortic cusp
13	Peery & Belter	Virginia	30	M	8	No	1:1280	Yes	Petechiae; spleen, pancreas, mesentery	Mitral, aortic	Fibrotic	Yes	Like Aschoff bodies	Cardiac	Pericarditis, ruptured cusp, lung infarcts
14	Peery & Belter	California	29	M	2	Heart disease	1:1280	Yes	Spleen; petechiae	Mitral	Calcified	No	Perivascular infiltration	Febrile, cardiac	Pneumonia
15	Peery & Belter	Iowa	24	M	6		1:1280	No				No	No	Pulmonary embolism	Pulmonary infarct, granulomas of liver and spleen

were divided as follows among the decades: 21 to 30 years, 10 cases; 31 to 40 years, 5 cases; 41 to 50 years, 9 cases; 51 to 60 years, 7 cases; 61 years or older, 3 cases; one case was designated simply as "adult."

The common mode of death in brucellar endocarditis is congestive heart failure rather than embolism or sepsis. Heart failure was noted in 60 per cent of all the cases of endocarditis.

Gross abscesses of the myocardium, or their equivalent, aneurysms, are apparently more frequent in brucellar endocarditis than in endocarditis due to other bacteria. This may well be correlated with the selective involvement of the aortic valve; abscesses are apparently more frequent in endocarditis of the semilunar valves than in that affecting atrioventricular valves. Abscesses occurred in 43 per cent of the cases with brucellar endocarditis, and in 58 per cent of those due to *Brucella abortus*.

Other inflammatory lesions of the myocardium were commonly encountered in fatal brucellosis. These lesions were focal, microscopic in size, paravascular, usually granulomatous and fibrotic, and often resembled Aschoff bodies. In 6 of the 12 fatal cases we have studied personally, myocardial lesions resembling Aschoff bodies were encountered. This can be compared with the incidence of Aschoff bodies in fatal rheumatic fever (32 to 87.5 per cent) as reported by various authors cited by Clawson.<sup>67</sup>

Brucellar endocarditis closely resembles calcareous disease of the aortic valve. Both show a remarkable prevalence in mature males. Brucellar endocarditis attacks the aortic valve selectively and produces a nodular, deforming lesion with a striking tendency to calcification. It is possible that the common valvular lesion, calcific aortic stenosis, believed by many to be a form of rheumatic heart disease, may occasionally be a sequel of brucellar endocarditis. For such a hypothesis to be considered, it must first be shown that endocarditis due to *Brucella* is not always fatal but may heal spontaneously, leaving a residual valvular lesion; this appears to be the case.<sup>68</sup> Analysis of other pertinent data suggests that brucellosis may in fact be the chief cause of calcific aortic stenosis.<sup>69</sup>

The observations cited would appear to justify the following conclusions:

1. The usual cause of death during brucellosis is endocarditis. In some instances myocarditis and pericarditis are evident.
2. Fatal *Brucella* endocarditis is essentially a chronic disease, with a greater tendency toward fibrosis, hyalinization and calcification than is usually noted in endocarditis caused by other bacteria. Because of these

features, most patients die from valve deformity and congestive heart failure rather than from sepsis or embolism.

3. The disease chiefly affects the aortic valve. In infections due to *Brucella abortus*, the strain most often encountered in the United States, this valve is involved more than twice as frequently as all other valves combined. The reason for this affinity is not apparent.

4. A prevalence in males is probably attributable to the fact that serious brucellar cardiac lesions are usually a result of heavy, recurrent occupational exposure, as in farmers, meat packers and veterinarians.

5. The disease tends to occur in middle adult life. In *Brucella abortus* infection, the average age at death from endocarditis was 43 years. This late development may be due in part to a natural immunity in children and adolescents.<sup>70</sup> It may also mean that repeated infection over many years is necessary for the development of the endocarditis.

6. Lesions resembling Aschoff bodies are commonly found in the myocardium in fatal brucellosis. Even when there are no "typical" Aschoff bodies—and this is primarily a matter of individual interpretation—it is common to encounter focal accumulations of lymphocytes and mononuclear cells together with patchy areas of interstitial fibrosis.

7. The observation of chronic valvular heart disease and "Aschoff bodies" in fatal infections due to *Brucella* makes it imperative that "rheumatic fever" be re-evaluated. "Rheumatic fever" may well be a syndrome including several diseases having febrile episodes and a tendency to involve the joints and the heart.<sup>71</sup>

#### APPENDIX: REPORT OF NEW CASES

##### *Fatal Brucella Abortus Infections (Group 1)*

*Case 1.* (A.F.I.P. #569444; case 18, Table I.) A 63-year-old white male was ill for about 15 months with irregular fever and recurring chills. There was no history of contact with farm animals, drinking raw milk, or rheumatic fever. Physical examination disclosed evidence of stenosis and insufficiency of the aortic valve. The liver and spleen were readily palpated. A blood culture taken 3 weeks before death was positive for *Brucella*. The VDRL and Kolmer tests were negative; a Kahn test was 4 plus (16 units).

Death occurred unexpectedly 10 days after admission. The clinical impression was subacute bacterial endocarditis, with embolism, possibly to the coronary arteries.

Necropsy was performed by Dr. Chapman H. Binford at the United States Marine Hospital, Baltimore, Maryland. The heart weighed 620 gm., the hypertrophy being chiefly of the left ventricle. There was an old infarct of the left ventricular myocardium near the apex. The mitral valve showed some thickening of the base of the aortic cusp. All of the cusps of the aortic valve were thickened and calcified, showing both old and recent vegetations. The posterior and the right anterior cusps were fused, and their common commissure was displaced downward. There was a perforation 1.5 cm. in diameter in the posterior cusp of the aortic valve. Opening into the aorta, lateral to this perforation, there was a 2 cm. aneurysm in the myocardium. Microscopic sections of the vegetations revealed extensive calcium deposits within dense hyaline connective tissue (Fig. 1). Some fields also showed foci of necrosis within the valve cusp and surface deposits of fibrin. Smears demonstrated numerous short gram-negative bacilli. Random sections of the myocardium ex-

hibited focal paravascular lesions containing stringy conglomerates of fibrinoid substance and large spindle-shaped and pleomorphic cells; these lesions were considered to be indistinguishable from the Aschoff bodies of rheumatic fever (Figs. 2 and 3). Cultures of heart blood, aortic valve vegetations, liver and spleen revealed *Brucella abortus*. There were infarcts in the spleen and brain.

*Case 2.* (A.F.I.P. #279996; case 19, Table I.) A 54-year-old white dairy farmer noted a sudden spell of dyspnea and precordial pain about 30 months before his death and remained in bed for 2 days. About 15 months later, chest pain, dyspnea and edema appeared, and there were fever, chills and sweats. A harsh systolic murmur was heard over the entire precordium. Terminally there was also a diastolic aortic murmur. Death was a result of heart failure. Blood cultures were repeatedly positive for *Brucella abortus* during the last 5 months of life.

At necropsy the heart weighed 500 gm. There were rough, calcified plaques on the leaflets of the aortic valve; one commissure was destroyed. Microscopic sections of the valve showed micro-abscesses surrounded by hyaline connective tissue containing calcium deposits (Fig. 4). The myocardium was the seat of focal paravascular monocytic infiltration (Fig. 5). The liver exhibited cirrhosis, but no noteworthy lesions were observed in the other organs.

*Case 3.* (A.F.I.P. #276412; case 20, Table I.) A 59-year-old white ranch foreman died suddenly after a 10-week period of chills, fever and weight loss. Systolic and diastolic murmurs were heard at the cardiac apex and over the lower sternum. Serologic tests for syphilis, negative 4 years previously, were positive terminally. A blood culture was positive for *Brucella abortus*. An electrocardiogram showed changes suggestive of a remote antero-septal infarction.

At necropsy the heart weighed 900 gm. All of the valves except the aortic appeared normal. The aortic cusps were rigid, nodular and calcified; the valve was believed to be both stenotic and regurgitant. There was a 3 cm. aneurysm in the interventricular septum; this was thought to be a mycotic aneurysm of the left anterior descending coronary artery. The aorta showed gross and microscopic alterations characteristic of syphilitic aortitis. Microscopically, there was myocardial necrosis and a diffuse leukocytic infiltration in the region of an abscess. Adjacent branches of the coronary arteries were infiltrated with neutrophils, but no lesions resembling Aschoff nodules were noted. The spleen contained multiple infarcts, but the other organs, including the brain, were not remarkable.

#### *Fatal Brucella Melitensis Infections (Group 2)*

*Case 4.* (A.F.I.P. #58597; case 12, Table II.) A 48-year-old male had performed necropsies on a number of goats which had died of an unknown disease. His own illness lasted 10 months and was characterized by fever, chills, joint pains and weight loss. There was atrial fibrillation, but no murmurs were heard. The spleen was palpable. A blood culture yielded *Brucella melitensis*.

At necropsy, scattered petechiae were noted in the skin. The heart weighed 410 gm. Only the mitral valve was abnormal. This showed a mass of firm, grayish white endocardial vegetations which almost completely obliterated the valve opening. Microscopically, the vegetation was largely acellular and fibrinous, but it contained numerous calcium deposits (Fig. 6). There were focal cellular nodules in the myocardium and in the subendocardial zone of the left atrium (Fig. 7).

Cultures of the heart blood and spleen grew *Brucella melitensis*.

*Case 5.* (A.F.I.P. #64684; case 13, Table II.) A 43-year-old Mexican had a 4-month illness with dyspnea, edema, chills and fever. A systolic thrill and murmur were noted at the cardiac apex. A blood culture was negative.

At necropsy, the heart was about normal in size. The mitral valve was markedly thickened, somewhat soft, and showed an ulcerated hemorrhagic lesion on the atrial surface. Cultures taken from this area yielded *Brucella melitensis*. The available sections did not include the valvular lesion. A section of left ventricle showed only irregular fibrous scarring. Other organs contained no significant abnormality.

*Fatal Brucella suis Infections (Group 3)*

Case 6. (A.F.I.P. #288404; case 7, Table III.) A 60-year-old farmer was ill only 11 days with fever, weakness and headache. He was admitted in shock and died a few hours later.

At necropsy, the heart showed no abnormality. The spleen weighed 500 gm. and was quite soft. Postmortem cultures taken from the spleen yielded *Brucella suis*. The other necropsy findings were not significant.

*Fatal Brucella Infections, Exact Strain Uncertain (Group 4)*

Case 7. (A.F.I.P. #317214; case 4, Table IV.) A 54-year-old white dairy farmer complained of vague upper abdominal pain beginning 11 months before his death. Seven months later he had a "typical episode of myocardial infarction." For the last 2 months his illness was marked by chills and fever. Twenty years previously he had been told that he had a heart murmur. From age 42 to 48 years, he had suffered with recurrent migratory arthritis involving all the joints except the spine. There was atrial fibrillation, and systolic and mid-diastolic murmurs were heard in the third left interspace. A blood culture yielded *Brucella*; the strain was not identified. The patient died following a sudden period of unconsciousness.

At necropsy, the heart weighed 590 gm. The mitral valve was moderately stenotic, and the cusps were thick and calcified. All cusps of the aortic valve were thickened and calcified. The anterior descending branch of the left coronary artery was occluded by a fresh thrombus, and there was an old myocardial infarct near the apex of the left ventricle. Both coronary arteries exhibited extensive atheromatous changes. Random sections of the myocardium showed focal lesions resembling Aschoff bodies (Fig. 8). The other organs were not remarkable; there were no other infarcts.

*Fatal Probable Brucellosis (Group 5)*

Case 8. (A.F.I.P. #139068; case 11, Table V.) A 25-year-old soldier, a native of Illinois, had a febrile illness for 7 months. This developed while he was convalescing in England from a battle wound received one month earlier. At one time a blood serum agglutinated the *Brucella* antigen in a dilution of 1:10,000. Palpitation and weakness were conspicuous symptoms, but no murmurs were heard. Death was the result of heart failure.

At necropsy, the heart weighed 420 gm.; it was globular, flabby, and thrombi were adherent to the endocardium of both ventricles. The valves showed no lesions. Microscopically, the myocardium contained foci of intensive inflammation, and in some areas there were lesions resembling Aschoff bodies. Both femoral veins contained adherent thrombi which extended into the inferior vena cava. There were no pulmonary emboli, and the other organs showed only congestion. Postmortem cultures were negative.

Case 9. (Case 12, Table V.) A 51-year-old preacher-farmer had intermittent bouts of fever and arthritis for 18 months. A *Brucella* agglutination in the serum reached a peak of 1:10,240. Ten days before death, the patient developed severe anginal pain, dyspnea, and was found to have aortic insufficiency. Death was a result of heart failure.

At necropsy, the heart weighed 500 gm. At the left posterior commissure of the aortic valve there was a 1.5 cm., nodular, hyaline mass. The posterior cusp showed a ragged tear and a firm friable vegetation. The other cusps of the aortic valve were relatively normal, and the other valves were completely normal. Microscopically, there were no noteworthy lesions of the myocardium. Infarcts were noted in the lung, spleen and right kidney.

Case 10. (A.F.I.P. #613963; case 13, Table V. The records and slides on this case were made available through the kindness of Dr. Charles H. Lupton, formerly of the University of Virginia, now of the Department of Pathology at the University of Alabama.)

A 30-year-old farmer had an 8 months' illness marked by chills, fever, muscular aches, dyspnea and weakness. The titer for *Brucella* agglutinins in his blood rose during the illness from 1:160 to 1:1280. While he was under observation, systolic and diastolic murmurs appeared over the aortic area. The last few weeks of the illness were characterized by cardiac failure and petechiae.

At necropsy, the heart weighed 580 gm., and the epicardium was fibrin coated. The

tricuspid and pulmonic valves were normal. The mitral valve was somewhat thickened along its line of closure. The commissure between the right and the posterior aortic cusps was fibrotic, and there was an old rupture of the right aortic cusp near the commissure. In the sinus of Valsalva behind the ruptured cusp there was a 1 cm. aneurysm; on microscopic examination this was lined with endothelium. There were paravascular foci of mononuclear cells and lymphocytes simulating Aschoff nodules (Figs. 9 and 10). The valvular lesion was hyaline and fibrotic; there was no evidence of active necrosis or leukocytic exudate. There were evidences of an old embolism in several organs in the systemic circulation, and the lungs contained multiple infarcts.

*Case 11.* (Case 14, Table V. This case was first obtained from the files of the National Institutes of Health through the kindness of Dr. L. L. Ashburn; it is also case #26819 in the files of the Armed Forces Institute of Pathology.) This patient, a resident of California, was discharged from the United States Navy at age 22 years because of heart disease, the nature of which was not recorded. At 29 years he became ill with fever, precordial distress, dyspnea and cough. A presystolic thrill and rumble were noted at the cardiac apex. Agglutinins against *Brucella* were demonstrable in his blood at a titer of 1:1280. He died following a spell of dyspnea and violent coughing.

At necropsy, numerous petechiae were noted in the skin. The heart weighed 420 gm., and the right ventricle was hypertrophied. The mitral valve cusps were thickened and calcified; a large vegetation was present on both surfaces of its aortic cusp. The other valve orifices were apparently normal. Microscopic sections of the myocardium revealed perivascular and interstitial infiltration with lymphocytes and mononuclear cells. The only pertinent findings in other organs were 3 infarcts in the spleen.

*Case 12.* (A.F.I.P. #170106; case 15, Table V.) A 24-year-old white farmer-soldier had a 6 months' illness characterized by intermittent fever, cough and weakness, and terminally by chest pain and dyspnea. Examination of the heart was normal. Serum agglutination of *Brucella* was positive in a dilution of 1:1280.

At necropsy, the heart weighed 430 gm. but showed no abnormality, grossly or microscopically. The lungs contained recent infarcts and multiple massive emboli. The liver and spleen were enlarged and exhibited focal granulomas, but the other organs revealed no abnormalities.

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Except as indicated, the new cases in the foregoing appendix are from the Armed Forces Institute of Pathology. The cooperation and encouragement of Dr. Chapman H. Binford, Chief of the Section on Infectious Diseases, Armed Forces Institute of Pathology, are gratefully acknowledged.

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\* In this case death occurred 10 months after onset of symptoms and 4 months after surgery, according to personal correspondence with Dr. Knighton.

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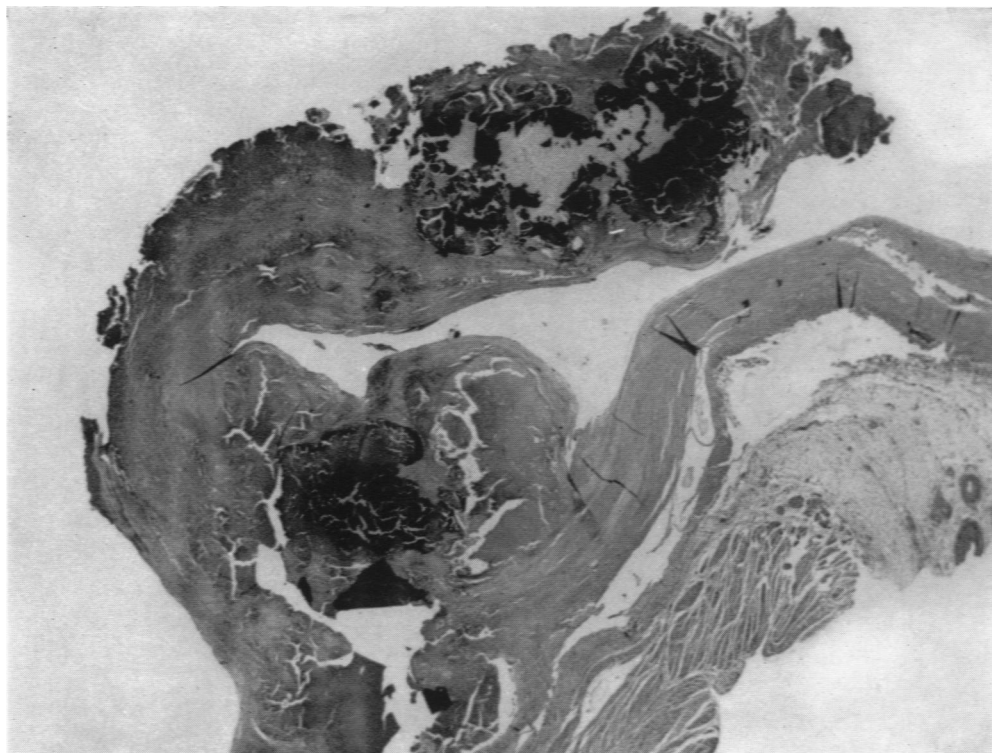
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#### LEGENDS FOR FIGURES

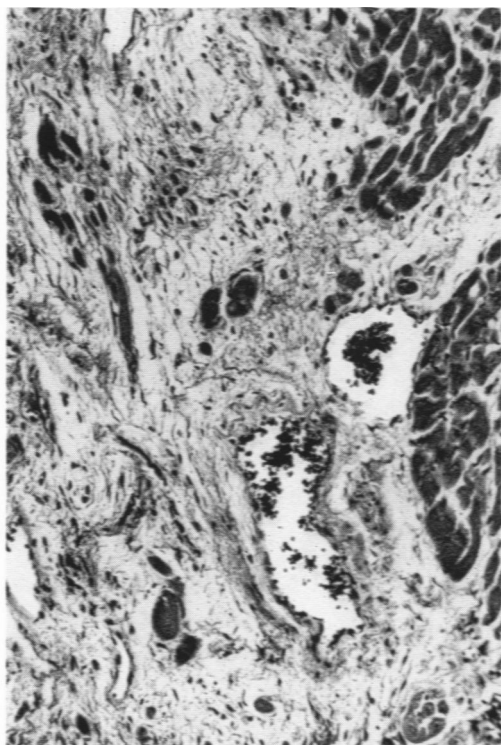
Photomicrographs were prepared from sections stained with hematoxylin and eosin.

- FIG. 1. A.F.I.P. #569444. Section of the aortic valve in a case of fatal endocarditis due to *Brucella abortus*. Large masses of calcium are noted in the free portion of the cusp (top) and at the base of the valve. Approximately  $\times 20$ .
- FIG. 2. A.F.I.P. #569444. Focal granulomatous lesions near small blood vessels in the myocardium of the left ventricle in fatal brucellar endocarditis. The lesion just to the left of center in the upper portion of the field is believed to meet the usual criteria for an "Aschoff body." \*  $\times 150$ .
- FIG. 3. A.F.I.P. #569444. Another lesion resembling an "Aschoff body" in a fatal case of endocarditis due to *Brucella abortus*. Wavy bands of "fibrinoid necrosis" are seen in the center of a granulomatous lesion. A small artery is transected at the left of the field.  $\times 300$ .

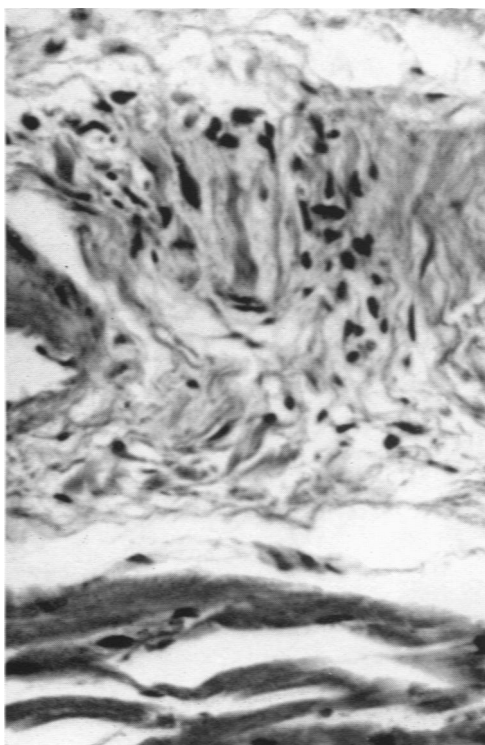
\* The Aschoff body is a lesion about which pathologists argue at length and sometimes bitterly. Photomicrographs from these cases have been shown to a large number of pathologists, and each has identified one or more lesions which he believes "typical"—but the selections differ. Since judgment in this matter is necessarily based upon preconceived criteria that cannot be proved by experimental or other methods, perhaps one shouldn't be too dogmatic in his opinions!



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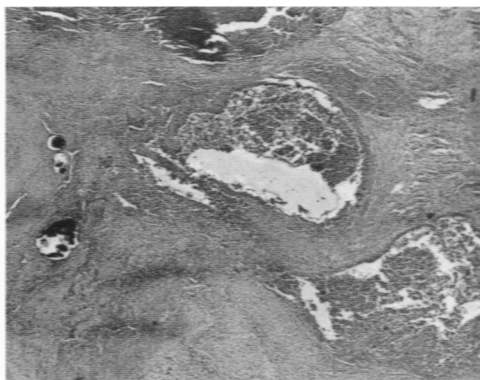
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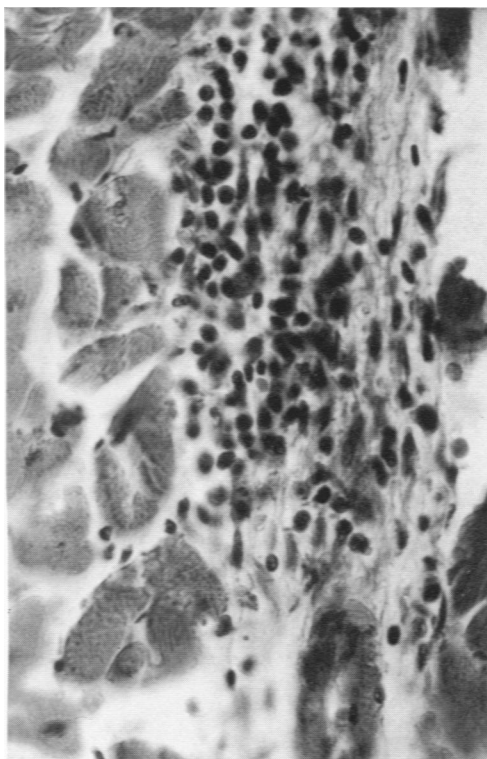
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- FIG. 4. A.F.I.P. #279996. Section through a nodular aortic valve lesion in a fatal case of endocarditis due to *Brucella abortus*. Two micro-abscesses appear in dense inflammatory tissue; minute calcium deposits are evident on the left. Approximately  $\times 60$ .
- FIG. 5. A.F.I.P. #279996. A focal paravascular inflammatory lesion of the myocardium in fatal brucellar endocarditis. This lesion is comparable to the active "granulomatous phase of the Aschoff body," described by others.  $\times 480$ .
- FIG. 6. A.F.I.P. #58597. A mitral valve lesion in a fatal case of *Brucella melitensis* endocarditis. The surface portion of the vegetation shows a cellular infiltrate, but the deeper portion is largely acellular and hyaline. Calcium deposits are noted in the lower right portion of the field.  $\times 80$ .
- FIG. 7. A.F.I.P. #58597. A focal granuloma of the myocardium in a case of *Brucella melitensis* endocarditis.  $\times 150$ .
- FIG. 8. A.F.I.P. #317214. A focal paravascular granuloma resembling an "Aschoff nodule" in the myocardium in a case of brucellar endocarditis (strain not identified).  $\times 150$ .
- FIG. 9. A.F.I.P. #613963. Focal paravascular lesions resembling "Aschoff bodies" in the myocardium in a case of endocarditis probably due to *Brucella*; cultures were negative, but the agglutination titer rose from 1:160 to 1:1280 under observation.  $\times 60$ .
- FIG. 10. A.F.I.P. #613963. Other myocardial lesions in a case of probable brucellar endocarditis. While the cellular infiltrate is somewhat diffuse, these lesions also resemble "Aschoff bodies."  $\times 180$ .

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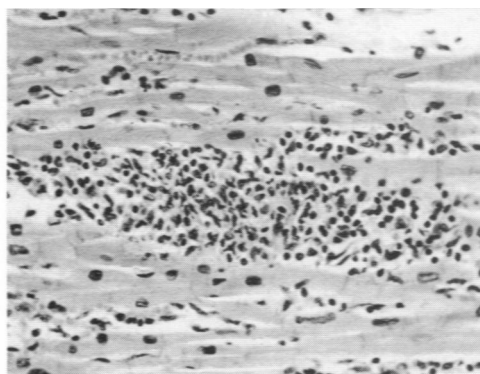
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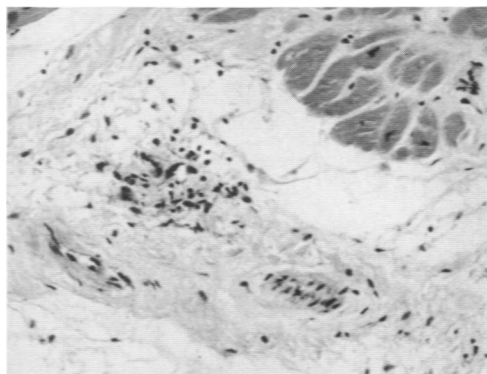
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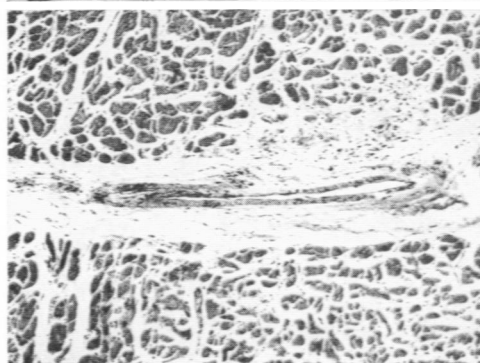
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